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=> s kinase (3A) transfection
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L4   ANSWER 1 OF 35     MEDLINE on STN                    DUPLICATE 1
AN   2005232469     IN-PROCESS
DN   PubMed ID: 15743775
TI   Protein kinase C activates human lipocalin-type prostaglandin D
synthase
     gene expression through de-repression of notch-HES signaling and
     enhancement of AP-2beta function in brain-derived TE671 cells.
AU   Fujimori Ko; Kadoyama Keiichi; Urade Yoshihiro
CS   Department of Molecular Behavioral Biology, Osaka Bioscience
Institute,
     6-2-4 Furuedai, Suita, Osaka 565-0874, Japan.
SO   Journal of biological chemistry, (2005 May 6) 280 (18) 18452-61.
     Electronic Publication: 2005-03-02.
     Journal code: 2985121R. ISSN: 0021-9258.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 20050504
     Last Updated on STN: 20050517
AB   Here we investigated the regulatory mechanism of lipocalin-type
     prostaglandin D synthase (L-PGDS) gene expression in human TE671
     (medulloblastoma of cerebellum) cells.  Reporter analysis of the
promoter
     region from -730 to +75 of the human L-PGDS gene demonstrated
that
     deletion or mutation of the N-box at -337 increased the promoter
activity
     220-300%.  The N-box was bound by Hes-1, a mammalian homologue of
     Drosophila Hairy and enhancer of split, as examined by
electrophoretic
     mobility shift assay and chromatin immunoprecipitation assay.
Functional
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expression of the Notch intracellular domain significantly increased Hes-1
expression and decreased L-PGDS expression level in TE671 cells. Moreover, knock-down of Hes-1 mRNA by RNA interference significantly
enhanced the L-PGDS mRNA level, indicating that the L-PGDS gene expression
is repressed by the Notch-Hes signaling. When the AP-2 element at -98 of
the promoter region was deleted or mutated, the promoter activity was
drastically decreased to approximately 10% of normal. The AP-2 element
was bound by AP-2beta dominantly expressed in TE671 cells, according to
the results of electrophoretic mobility shift assay and chromatin immunoprecipitation assay. L-PGDS expression was induced by
12-O-tetradecanoylphorbol-13-acetate in TE671 cells, and this induction
was inhibited by a protein **kinase** C **inhibitor**.
Stimulation of TE671 cells with 12-O-tetradecanoylphorbol-13-acetate or
transfection with protein **kinase** Calpha expression
vector induced **phosphorylation** of Hes-1, inhibition of DNA
binding of Hes-1 to the N-box, and activation of the AP-2beta function to
up-regulate L-PGDS gene expression. These results reveal a novel transcriptional regulatory mechanism responsible for the high level
expression of the human L-PGDS gene in TE671 cells.

L4 ANSWER 2 OF 35 EMBASE
on STN
AN 2005172674 EMBASE
TI The pro-inflammatory mediator leukotriene D(4) induces phosphatidylinositol 3-kinase and Rac-dependent migration of intestinal
epithelial cells.
AU Paruchuri S.; Broom O.; Dib K.; Sjolander A.
CS A. Sjolander, Dept. of Laboratory Medicine, Lund University, Malmo
University Hospital, Entrance 78, SE-205 02 Malmo, Sweden.
anita.sjolander@exppat.mas.lu.se
SO Journal of Biological Chemistry, (8 Apr 2005) Vol. 280, No. 14, pp.
13538-13544.
Refs: 41
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy

016 Cancer
048 Gastroenterology
LA English
SL English
ED Entered STN: 20050519
Last Updated on STN: 20050519
AB Inflammatory bowel diseases are associated with increased risk of developing colon cancer. A possible role of the pro-inflammatory leukotriene D(4) (LTD(4)) in this process has been implicated by the findings that LTD(4) can signal increased proliferation and survival, both hallmarks of a cancer cell, in non-transformed intestinal epithelial cells. Here we make the novel finding that LTD(4) can also signal increased motility in these cells. In parallel, we found that LTD(4) induced a simultaneous transient 10-fold increase in Rac but not Cdc42 activity. These data were also supported by the ability of LTD(4) to activate the Rac GDP/GTP exchange factor Vav2. Further, LTD(4) triggered a 3-fold transient increase in phosphatidylinositol 3-kinase (PI3K) **phosphorylation**, a possible upstream activator of the Vav2/Rac signaling pathway. The activation of Rac was blocked by the PI3K inhibitors LY294002 and wortmannin and by **transfection** of a **kinase**-negative mutant of PI3K or a dominant-negative form of Vav2. Furthermore, Rac was found to co-localize with actin in LTD (4)-generated membrane ruffles that were formed by a PI3K-dependent mechanism. In accordance, the inhibition of the PI3K and Rac signaling pathway also blocked the LTD(4)-induced migration of the intestinal cells. The present data reveal that an inflammatory mediator such as LTD(4) cannot only increase proliferation and survival of non-transformed intestinal epithelial cells but also, via a PI3K/Rac signaling pathway, trigger a motile response in such cells. These data demonstrate the capacity of inflammatory mediators to participate in the process by which inflammatory bowel conditions increase the risk for colon cancer development.

L4 ANSWER 3 OF 35 MEDLINE on STN DUPLICATE 2
AN 2005208403 MEDLINE
DN PubMed ID: 15843032
TI Leukemia inhibitory factor blocks early differentiation of skeletal muscle
cells by activating ERK.
AU Jo Chulman; Kim Hyuck; Jo Inho; Choi Insun; Jung Sung-Chul; Kim Joon; Kim
Sung Soo; Jo Sangmee Ahn
CS Department of Biomedical Sciences, National Institute of Health, Seoul,
South Korea.
SO Biochimica et biophysica acta, (2005 Apr 15) 1743 (3) 187-97. Electronic
Publication: 2004-12-08.
Journal code: 0217513. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200506
ED Entered STN: 20050422
Last Updated on STN: 20050610
Entered Medline: 20050609
AB Leukemia inhibitory factor (LIF) is a multifunctional cytokine belonging
to the interleukin-6 family and has been shown to stimulate regeneration
of injured skeletal muscle. Although LIF has been shown to stimulate
muscle cell proliferation, its precise role in differentiation is unclear.
Thus, we examined the effect of LIF on the differentiation of cultured
C2C12 myoblast cells. In this study, we used both non-glycosylated LIF
expressed in bacteria and glycosylated LIF secreted from NIH3T3 cells
infected with Ad-LIF. Both non-glycosylated and glycosylated LIF blocked
differentiation of myoblasts as measured by expression of myosin heavy
chain and myotube formation. Treatment of myoblasts with LIF induced
phosphorylation of ERK, and the LIF-induced inhibitory effect on
myogenesis was blocked by pretreatment with U0126, a specific MEK
inhibitor, and transient transfection with dominant negative (DN)-MEK1.
In contrast, although LIF activated STAT3, the LIF-induced repression of
the MCK transcriptional activity was not reversed by pretreatment with

AG490, a specific Jak **kinase inhibitor** or transient **transfection** with DN-STAT3. Additionally, LIF exhibited its inhibitory effect on myogenesis only when cells were treated at earlier than 12 h after inducing differentiation. Taken together, these results suggest that LIF strongly inhibited early myogenic differentiation though activation of the ERK signaling pathway and its effect is irrespective of glycosylation.

L4 ANSWER 4 OF 35 MEDLINE on STN DUPLICATE 3
AN 2004319053 MEDLINE
DN PubMed ID: 15123725
TI Hepatic nuclear factor 3 and nuclear factor 1 regulate 5-aminolevulinate synthase gene expression and are involved in insulin repression.
AU Scassa Maria E; Guberman Alejandra S; Ceruti Julieta M; Canepa Eduardo T
CS Laboratorio de Biologia Molecular, Departamento de Quimica Biologica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellon II Piso 4, Ciudad Universitaria, 1428 Buenos Aires, Argentina.
SO Journal of biological chemistry, (2004 Jul 2) 279 (27) 28082-92. Electronic Publication: 2004-04-28. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200408
ED Entered STN: 20040629 Last Updated on STN: 20040812 Entered Medline: 20040811
AB Although the negative regulation of gene expression by insulin has been widely studied, the transcription factors responsible for the insulin effect are still unknown. The purpose of this work was to explore the molecular mechanisms involved in the insulin repression of the 5-aminolevulinate synthase (ALAS) gene. Deletion analysis of the 5'-regulatory region allowed us to identify an insulin-responsive region located at -459 to -354 bp. This fragment contains a highly homologous insulin-responsive (IRE) sequence. By transient transfection assays, we determined that hepatic nuclear factor 3 (HNF3) and nuclear factor 1 (NF1)

are necessary for an appropriate expression of the ALAS gene. Insulin overrides the HNF3beta or HNF3beta plus NF1-mediated stimulation of ALAS transcriptional activity. Electrophoretic mobility shift assay and Southwestern blotting indicate that HNF3 binds to the ALAS promoter. Mutational analysis of this region revealed that IRE disruption abrogates insulin action, whereas mutation of the HNF3 element maintains hormone responsiveness. This dissociation between HNF3 binding and insulin action suggests that HNF3beta is not the sole physiologic mediator of insulin-induced transcriptional repression. Furthermore, Southwestern blotting assay shows that at least two polypeptides other than HNF3beta can bind to ALAS promoter and that this binding is dependent on the integrity of the IRE. We propose a model in which insulin exerts its negative effect through the disturbance of HNF3beta binding or transactivation potential, probably due to specific **phosphorylation** of this transcription factor by Akt. In this regard, results obtained from **transfection** experiments using **kinase inhibitors** support this hypothesis. Due to this event, NF1 would lose accessibility to the promoter. The posttranslational modification of HNF3 would allow the binding of a protein complex that recognizes the core IRE. These results provide a potential mechanism for the insulin-mediated repression of IRE-containing promoters.

L4 ANSWER 5 OF 35 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 2004411440 EMBASE
TI PKCα induces differentiation through ERK1/2 **phosphorylation** in mouse keratinocytes.
AU Seo H.R.; Kwan Y.-W.; Cho C.-K.; Bae S.; Lee S.-J.; Soh J.-W.; Chung H.-Y.; Lee Y.-S.
CS Y.-S. Lee, Laboratory of Radiation Effect, Korea Inst. of Radiol. and Med. Sci., 215-4 Gongneung-dong, Nowon-Ku, Seoul 139-706, Korea, Republic of.
yslee@kcch.re.kr
SO Experimental and Molecular Medicine, (31 Aug 2004) Vol. 36, No. 4, pp.

292-299.
Refs: 41
ISSN: 1226-3613 CODEN: EMMEF3
CY Korea, Republic of
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 20041018
Last Updated on STN: 20041018
AB Epidermal keratinocyte differentiation is a tightly regulated stepwise process that requires protein kinase C (PKC) activation. Studies on cultured mouse keraitnocytes induced to differentiate with Ca(2+) have indirectly implicated the involvement of PKCα isoform. When PKCα was overexpressed in undifferentiated keratinocytes using adenoviral system, expressions of differentiation markers such as loricrin, filaggrin, keratin 1 (MK1) and keratin 10 (MK10) were increased, and ERK1/2 **phosphorylation** was concurrently induced without change of other MAPK such as p38 MAPK and JNK1/2. Similarly, **transfection** of PKCα **kinase** active mutant (PKCα-CAT) in the undifferentiated keratinocyte, but not PKCβ-CAT, also increased differentiation marker expressions. On the other hand, PKCα dominant negative mutant (PKCβ-KR) reduced Ca(2+)-mediated differentiation marker expressions, while PKCβ-KR did not, suggesting that PKCα is responsible for keratinocyte differentiation. When downstream pathway of PKCα in Ca(2+)-mediated differentiation was examined, ERK1/2, p38 MAPK and JNK1/2 **phosphorylations** were increased by Ca(2+) shift. Treatment of keratinocytes with PD98059, MEK inhibitor, and SB20358, p38 MAPK inhibitor, before Ca(2+) shift induced morphological changes and reduced expressions of differentiation markers, but treatment with SP60012, JNK1/2 inhibitor, did not change at all. Dominant negative mutants of ERK1/2 and p38 MAPK also inhibited the expressions of differentiation marker expressions in Ca(2+) shifted cells. The above results indicate that both ERK1/2 and p38 MAPK may be involved in Ca(2+)-mediated differentiation, and that only ERK1/2 pathway is specific for PKCα-mediated differentiation in mouse keratinocytes.

L4 ANSWER 6 OF 35 EMBASE

on STN
AN 2004128156 EMBASE
TI Myosin light chain **phosphorylation** and pulmonary endothelial cell hyperpermeability in burns.
AU Tinsley J.H.; Teasdale N.R.; Yuan S.Y.
CS J.H. Tinsley, Dept. of Medical Physiology, TX A/M Univ. Syst. Hlth. Sci.
Ctr., 702 SW HK Dodgen Loop, Temple, TX 76504, United States. jht@tamu.edu
SO American Journal of Physiology - Lung Cellular and Molecular Physiology,
(2004) Vol. 286, No. 4 30-4, pp. L841-L847.
Refs: 32
ISSN: 1040-0605 CODEN: APLPE7
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20040422
Last Updated on STN: 20040422
AB Major cutaneous burns result in not only localized tissue damage but broad
systemic inflammation causing organ system damage distal to the burn site.
It is well recognized that many problems result from the release of
inflammatory mediators that target vascular endothelial cells, causing
organ dysfunction. The pulmonary microvessels are particularly
susceptible to functional abnormalities as a direct consequence of
exposure to burn-induced inflammatory mediators. Traditional therapeutic
intervention is quite often ineffective in treating burn patients
suffering from systemic problems. A possible explanation for this
ineffectiveness may be that because so many mediators are released,
supposedly activating numerous signaling cascades that interact with each
other, targeting of upstream factors in these cascades on an individual
basis becomes futile. Therefore, if an end-point effector responsible for
endothelial dysfunction following burn injury could be identified, it may
present a target for intervention. In this study, we identified
phosphorylation of myosin light chain (MLC) as a required element
of burn plasma-induced hyperpermeability across rat lung microvascular

endothelial cell monolayers. In addition, pharmacological inhibition of myosin light chain kinase (MLCK) and Rho **kinase** as well as **transfection** of MLCK-inhibiting peptide blocked actin stress fiber formation and MLC **phosphorylation** in response to burn plasma. The results suggest that blocking MLC **phosphorylation** may provide therapeutic intervention in burn patients with the goal of alleviating systemic inflammation-induced endothelial dysfunction.

L4 ANSWER 7 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:42090 CAPLUS
DN 138:100897
TI Use of tyrosine **kinase inhibitors** for treating inflammatory bowel diseases (IBD)
IN Moussy, Alain; Kinet, Jean-Pierre
PA AB Science, Fr.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003004007	A2	20030116	WO 2002-IB3317	20020628
WO 2003004007	A3	20030828		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452392	AA	20030116	CA 2002-2452392	20020628
EP 1401416	A2	20040331	EP 2002-758697	20020628

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004537542 T2 20041216 JP 2003-510018 20020628
US 2004266801 A1 20041230 US 2004-482033 20040707
PRAI US 2001-301405P P 20010629
WO 2002-IB3317 W 20020628
OS MARPAT 138:100897
AB The present invention relates to a method for treating inflammatory bowel diseases (IBD), such as Crohn's disease, comprising administering a tyrosine **kinase inhibitor** to a human in need of such treatment, more particularly a non-toxic, selective and potent c-kit inhibitor. Preferably, said inhibitor is unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

L4 ANSWER 8 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:22675 CAPLUS
DN 138:95588
TI Use of tyrosine **kinase inhibitors** for treating multiple sclerosis
IN Moussy, Alain; Kinet, Jean-Pierre
PA AB Science, Fr.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002107	A2	20030109	WO 2002-IB3298	20020628
WO 2003002107	A3	20031002		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2452167 AA 20030109 CA 2002-2452167 20020628
EP 1401414 A2 20040331 EP 2002-758692 20020628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2005502614 T2 20050127 JP 2003-508346 20020628
US 2004259892 A1 20041223 US 2003-482034 20031229
PRAI US 2001-301409P P 20010629
WO 2002-IB3298 W 20020628
OS MARPAT 138:95588
AB The present invention relates to a method for treating Multiple Sclerosis
(MS) comprising administering a tyrosine **kinase inhibitor** to a human in need of such treatment, more particularly a non-toxic, selective and potent c-kit inhibitor. Preferably said
inhibitor is unable to promote death of IL-3 dependent cells cultured in
presence of IL-3.

L4 ANSWER 9 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:22674 CAPLUS
DN 138:83364
TI Use of tyrosine kinase inhibitions for treating allergic diseases
IN Moussy, Alain; Kinet, Jean-Pierre
PA AB Science, Fr.
SO PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002106	A2	20030109	WO 2002-IB3297	20020628
WO 2003002106	A3	20030530		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
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UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2452371	AA	20030109	CA 2002-2452371	20020628
EP 1401413	A2	20040331	EP 2002-755512	20020628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004537536	T2	20041216	JP 2003-508345	20020628
US 2004259893	A1	20041223	US 2003-482035	20031229
PRAI US 2001-301408P	P	20010629		
WO 2002-IB3297	W	20020628		

OS MARPAT 138:83364

AB The present invention relates to a method for treating allergic diseases such as asthma, comprising administering a tyrosine **kinase inhibitor** to a human in need of such treatment, more particularly a non-toxic, selective and potent c-kit inhibitor. Preferably, said inhibitor is unable to promote death of IL-3 dependent cells cultured in presence of IL-3.

L4 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:22673 CAPLUS
DN 138:95587
TI Use of tyrosine **kinase inhibitors** for treating bone loss
IN Moussy, Alain; Kinet, Jean-Pierre
PA AB Science, Fr.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 13

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2003002105 A2 20030109 WO 2002-IB3288 20020628
WO 2003002105 A3 20030828
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PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2452390 AA 20030109 CA 2002-2452390 20020628
EP 1401411 A2 20040331 EP 2002-755506 20020628
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004530722 T2 20041007 JP 2003-508344 20020628
US 2004266771 A1 20041230 US 2004-482036 20040713
PRAI US 2001-301411P P 20010629
WO 2002-IB3288 W 20020628
OS MARPAT 138:95587
AB The present invention relates to a method for treating bone loss such as
osteoporosis comprising administering a tyrosine **kinase inhibitor** to a human in need of such treatment, more particularly a non-toxic, selective and potent c-kit inhibitor. Preferably, said
inhibitor is unable to promote death of IL-3 dependent cells cultured in
presence of IL-3.

L4 ANSWER 11 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:536960 CAPLUS
DN 139:163424
TI T-cell-derived Interleukin-17 Regulates the Level and Stability of
Cyclooxygenase-2 (COX-2) mRNA through Restricted Activation of the p38

Mitogen-activated Protein Kinase Cascade: Role of Distal Sequences in the 3'-Untranslated Region of COX-2 mRNA

AU Faour, Wissam H.; Mancini, Arturo; He, Qing Wen; Di Battista, John A.
CS Molecular Biology Program, University of Montreal, Montreal, QC, H3A 1A1, Can.

SO Journal of Biological Chemistry (2003), 278(29), 26897-26907
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English

AB Although interleukin-17 (IL-17) is the pre-eminent T-cell-derived pro-inflammatory cytokine, its cellular mechanism of action remains poorly understood. The authors explored novel signaling pathways mediating IL-17 induction of the cyclooxygenase-2 (COX-2) gene in human chondrocytes, synovial fibroblasts, and macrophages. In preliminary work, recombinant human (rh) IL-17 stimulated a rapid (5-15 min), substantial (>8-fold), and sustained (>24 h) increase in COX-2 mRNA, protein, and prostaglandin E2 release. Screening expts. with cell-permeable **kinase inhibitors** (e.g. SB202190 and p38 inhibitor), Western anal. using specific anti-phospho-antibodies to a variety of mitogen-activated protein **kinase** cascade intermediates, co-**transfection** studies using chimeric cytomegalovirus-driven constructs of GAL4 DNA-binding domains fused to the transactivation domains of transcription factors together with Gal-4 binding element-luciferase reporters, ectopic overexpression of activated protein kinase expression plasmids (e.g. MKK3/6), or transfection expts. with wild-type and mutant COX-2 promoter constructs revealed that rhIL-17 induction of the COX-2 gene was mediated exclusively by the stress-activated protein kinase 2/p38 cascade. A rhIL-17-dependent transcriptional pulse (1.76-fold induction) was initiated by ATF-2/CREB-1 transactivation through the ATF/CRE enhancer site in the proximal promoter. However, steady-state levels of rhIL-17-induced COX-2 mRNA declined rapidly (<2 h) to control levels under wash-out conditions. Adding rhIL-17 to transcriptionally arrested cells

stabilized COX-2 mRNA for up to 6 h, a process compromised by SB202190.
Deletion anal. using transfected chimeric luciferase-COX-2 mRNA 3'-untranslated region reporter constructs revealed that rhIL-17 increased
reporter gene mRNA stability and protein synthesis via distal regions
(-545 to -1414 bases) of the 3'-untranslated region. This response was
mediated entirely by the stress-activated protein kinase 2/p38 cascade.
As such, IL-17 can exert direct transcriptional and post-transcriptional
control over target proinflammatory cytokines and oncogenes.
RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 35 MEDLINE on STN DUPLICATE 4
AN 2003304429 MEDLINE
DN PubMed ID: 12730223
TI Fibronectin fragment activation of proline-rich tyrosine kinase PYK2
mediates integrin signals regulating collagenase-3 expression by human
chondrocytes through a protein kinase C-dependent pathway.
AU Loeser Richard F; Forsyth Christopher B; Samarel Allen M; Im Hee-Jeong
CS Department of Internal Medicine, Rush Medical College,
Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612,
USA.. rloeser@rush.edu
NC AR49003 (NIAMS)
HL63711 (NHLBI)
P50-AR39239 (NIAMS)
SO Journal of biological chemistry, (2003 Jul 4) 278 (27) 24577-85.
Electronic Publication: 2003-04-30.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030701
Last Updated on STN: 20030819
Entered Medline: 20030818
AB Fibronectin fragments (FN-f), including the 110-kDa fragment that binds
the alpha5beta1 integrin, stimulate collagenase-3 (MMP-13) production and
cartilage destruction. In the present study, treatment of chondrocytes
with the 110-kDa FN-f or an activating antibody to the alpha5beta1

integrin was found to increase tyrosine autophosphorylation (Tyr-402) of the proline-rich tyrosine kinase-2 (PYK2) without significant change in autophosphorylation (Tyr-397) of focal adhesion kinase (FAK). The tyrosine **kinase inhibitor** tyrphostin A9, shown previously to block a PYK2-dependent pathway, blocked the FN-f-stimulated increase in MMP-13, whereas tyrphostin A25 did not. FN-f-stimulated PYK2 **phosphorylation** and MMP-13 production was also blocked by reducing intracellular calcium levels. Adenovirally mediated overexpression of wild type but not mutant PYK2 resulted in increased MMP-13 production. The protein kinase C (PKC) activator phorbol 12-myristate 13-acetate stimulated PYK2 **phosphorylation** and MMP-13 production. MMP-13 expression stimulated by either phorbol 12-myristate 13-acetate or FN-f was blocked by PKC inhibitors including the PKCdelta inhibitor rottlerin. Furthermore, PKCdelta translocation from cytosol to membrane was noted within 5 min of stimulation with FN-f. Immortalized human chondrocytes, transiently transfected with MMP-13 promoter-luciferase reporter constructs, showed increased promoter activity after FN-f treatment that was inhibited by co-transfection with either of two dominant negative mutants of PYK2 (Y402F and K457A). No inhibition was seen after cotransfection with wild type PYK2, a dominant negative of FAK (FRNK) or empty vector plasmid. FN-f-stimulated MMP-13 promoter activity was also inhibited by chemical inhibitors of ERK, JNK, and p38 mitogen-activated protein (MAP) **kinases** or by co-**transfection** of dominant negative MAP kinase mutant constructs. These studies have identified a novel pathway for the MAP kinase regulation of MMP-13 production which involves FN-f stimulation of the alpha5beta1 integrin and activation of the nonreceptor tyrosine kinase PYK2 by PKC, most likely PKCdelta

AN 2003040930 MEDLINE
DN PubMed ID: 12431978
TI Src kinase mediates phosphatidylinositol 3-kinase/Akt-dependent rapid
endothelial nitric-oxide synthase activation by estrogen.
AU Haynes M Page; Li Lei; Sinha Diviya; Russell Kerry S; Hisamoto Koji; Baron
Roland; Collinge Mark; Sessa William C; Bender Jeffrey R
CS Section of Cardiovascular Medicine, Department of Pharmacology, Boyer
Center for Molecular Medicine, Yale University School of Medicine, New
Haven, Connecticut 06536, USA.
NC HL61782 (NHLBI)
SO Journal of biological chemistry, (2003 Jan 24) 278 (4) 2118-23.
Electronic Publication: 2002-11-12.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200303
ED Entered STN: 20030129
Last Updated on STN: 20030305
Entered Medline: 20030304
AB 17beta-Estradiol activates endothelial nitric oxide synthase (eNOS),
enhancing nitric oxide (NO) release from endothelial cells via the
phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway. The upstream
regulators of this pathway are unknown. We now demonstrate that
17beta-estradiol rapidly activates eNOS through Src kinase in human
endothelial cells. The Src family **kinase** specific-
inhibitor 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-
d]pyrimidine (PP2) abrogates 17beta-estradiol- but not
ionomycin-stimulated NO release. Consistent with these results, PP2
blocked 17beta-estradiol-induced Akt **phosphorylation** but did not
inhibit NO release from cells transduced with a constitutively active Akt.
PP2 abrogated 17beta-estradiol-induced activation of PI3-kinase,
indicating that the PP2-inhibitable kinase is upstream of PI3-kinase and
Akt. A 17beta-estradiol-induced estrogen receptor/c-Src association
correlated with rapid c-Src **phosphorylation**. Moreover,
transfection of **kinase**-dead c-Src inhibited
17beta-estradiol-induced Akt **phosphorylation**, whereas
constitutively active c-Src increased basal Akt **phosphorylation**.
Estrogen stimulation of murine embryonic fibroblasts with homozygous

deletions of the c-src, fyn, and yes genes failed to induce Akt **phosphorylation**, whereas cells maintaining c-Src expression demonstrated estrogen-induced Akt activation. Estrogen rapidly activated c-Src inducing an estrogen receptor, c-Src, and P85 (regulatory subunit of PI3-kinase) complex formation. This complex formation results in the successive activation of PI3-kinase, Akt, and eNOS with consequent enhanced NO release, implicating c-Src as a critical upstream regulator of the estrogen-stimulated PI3-kinase/Akt/eNOS pathway.

L4 ANSWER 14 OF 35 MEDLINE on STN DUPLICATE 6
AN 2003361838 MEDLINE
DN PubMed ID: 12824296
TI Arg-Gly-Asp-Ser (RGDS) peptide stimulates transforming growth factor beta1 transcription and secretion through integrin activation.
AU Ortega-Velazquez R; Diez-Marques M L; Ruiz-Torres M P; Gonzalez-Rubio M; Rodriguez-Puyol M; Rodriguez Puyol D
CS Department of Physiology, Alcala University, Nephrology Section, Hospital Principe de Asturias, and IRSIN, Madrid, Spain.
SO FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2003 Aug) 17 (11) 1529-31. Electronic Publication: 2003-06-03. Journal code: 8804484. ISSN: 1530-6860.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200308
ED Entered STN: 20030805
Last Updated on STN: 20030812
Entered Medline: 20030811
AB Extracellular matrix (ECM) components, through specific peptide motifs such as Arg-Gly-Asp (RGD), interact with integrins and can modify the behavior of cells. Transforming growth factor-beta1 (TGF-beta1) is the main cytokine involved in the synthesis of ECM proteins. We analyzed the effect of a RGD-containing peptide, as Arg-Gly-Asp-Ser (RGDS), on the regulation of TGF-beta1 secretion in cultured human mesangial cells. We found that RGDS increased mRNA expression and secretion of TGF-beta1 by

stimulating the TGF-beta1 gene promoter. This effect was dependent on the interaction of RGDS with integrins. We evaluated the signaling pathways implicated in TGF-beta1 production by analyzing the effect of RGDS on kinase-related integrins. RGDS stimulated tyrosine **phosphorylation** as well as integrin-linked kinase (ILK) activity. However, tyrosine **kinase inhibitors** did not prevent the RGDS effect. In contrast, the inhibition of ILK by cell **transfection** with a **kinase** dead-ILK completely abolished the increased TGF-beta1 secretion and promoter activity in the presence of RGDS. Thus RGDS modulates the secretion of TGF-beta1, probably through increased synthesis by interacting with integrins and activating ILK. This supports a role for ECM components in the regulation of their own secretion.

L4 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:87759 CAPLUS
DN 138:351913
TI ErbB-2 signaling is involved in regulating PSA secretion in androgen-independent human prostate cancer LNCaP C-81 cells
AU Lee, Ming-Shyue; Igawa, Tsukasa; Yuan, Ta-Chun; Zhang, Xiu-Qing; Lin, Fen-Fen; Lin, Ming-Fong
CS Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE, 68198, USA
SO Oncogene (2003), 22(5), 781-796
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
AB The expression and secretion of prostate-specific antigen (PSA) are regulated by androgens in normal prostate secretory epithelial cells. In prostate cancer patients, the serum PSA level is usually elevated and cancer cells are initially responsive to androgens. However, those cancer cells become androgen-independent after androgen ablation therapy. In hormone-refractory cancer patients, even in an androgen-deprived environment, the circulation level of PSA rebounds and is constitutively elevated through a yet unknown mechanism. Tyrosine **phosphorylation** of ErbB-2 is involved in regulating the

androgen-responsive phenotype of prostate cancer cells, and it is at least partly regulated by the cellular form of prostatic acid phosphatase (PAcP), a prostate-unique protein tyrosine phosphatase. We investigated the ErbB-2 signal pathway in androgen-independent PSA secretion. LNCaP C-81 cells, which are androgen-independent LNCaP cells lacking endogenous PAcP expression with a hyper-tyrosine phosphorylated ErbB-2, secreted a higher level of PSA in conditioned media than did androgen-sensitive LNCaP C-33 parental cells. A restored expression of cellular PAcP in C-81 cells was concurrent with a decrease in tyro-**phosphorylation** of ErbB-2 and reduction of PSA secretion. Moreover, transient transfection of C-33 cells with the wild-type ErbB-2 or a constitutively active mutant of MEK1 cDNA resulted in an increased level of secreted PSA. The elevation of secreted PSA level by the forced expression of ErbB-2 was inhibited by an MEK inhibitor, PD98059. In C-81 cells, the expression of a dominant neg. mutant of ErbB-2 reduced the secreted level of PSA. The inhibition of ErbB-2 or mitogen-activated protein (MAP) **kinases** by specific **inhibitors** AG879, AG825, or PD98059 led to a decrease in PSA secretion. Taken together, our data clearly indicate that the ErbB-2 signal pathway via MAP kinases (ERK1/2) is involved in regulating the secretion of PSA by androgen-independent human prostate cancer LNCaP C-81 cells in an androgen-depleted environment.

RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 35 EMBASE
on STN DUPLICATE 7
AN 2003084542 EMBASE
TI Altered protein kinase C (PKC) isoforms in non-small cell lung cancer cells: PKCδ promotes cellular survival and chemotherapeutic resistance.
AU Clark A.S.; West K.A.; Blumberg P.M.; Dennis P.A.
CS P.A. Dennis, Cancer Therapeutics Branch, National Cancer Institute,

Building 8, 8901 Wisconsin Avenue, Bethesda, MD 20889, United States.
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SO Cancer Research, (15 Feb 2003) Vol. 63, No. 4, pp. 780-786.
Refs: 36
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20030313
Last Updated on STN: 20030313
AB Drugs that target protein kinase C (PKC) are now being evaluated in patients with non-small cell lung cancer (NSCLC), but the role of PKC in NSCLC cells remains unclear. We report here that NSCLC cell lines show enhanced **phosphorylation** and altered expression of specific PKC isoforms compared with normal lung epithelial cells. PKC inhibition variably increased apoptosis, with rottlerin, a PKCδ inhibitor, being most effective and potentiating chemotherapy-induced apoptosis, especially with trastuzumab. Consistent with PKCδ being anti-apoptotic in NSCLC cells, transient **transfection** of a **kinase**-dead mutant of PKCδ increased apoptosis and potentiated chemotherapy-induced apoptosis. Our studies provide a rationale for targeting PKC isoforms in NSCLC cells, especially PKCδ.

L4 ANSWER 17 OF 35 MEDLINE on STN DUPLICATE 8
AN 2002428799 MEDLINE
DN PubMed ID: 12185584
TI Rho-kinase contributes to diphosphorylation of myosin II regulatory light chain in nonmuscle cells.
AU Ueda Kozue; Murata-Hori Maki; Tatsuka Masaaki; Hosoya Hiroshi
CS Department of Biological Science, Graduate School of Science, Hiroshima University, Higashi-Hiroshima, 739-8526, Japan.
SO Oncogene, (2002 Aug 29) 21 (38) 5852-60.
Journal code: 8711562. ISSN: 0950-9232.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 20020820

Last Updated on STN: 20020906
Entered Medline: 20020905

AB **Phosphorylation** of myosin II regulatory light chain (MRLC) is important for cell motility and cytokinesis in nonmuscle cells. Although the regulation of monophosphorylated MRLC at serine 19 throughout the cell cycle was examined in detail, MRLC diphosphorylation at both threonine 18 and serine 19 is still unclear. Here we found that Rho-kinase has an activity for MRLC diphosphorylation in nonmuscle cells using sequential column chromatographies. **Transfection** of Rho-**kinase** -EGFP induced the excess diphosphorylated MRLC and the bundling of the actin filaments. Conversely, the treatment of cells with a specific **inhibitor** of Rho-**kinase**, Y-27632, resulted in the decrease of endogenous diphosphorylated MRLC and actin stress fibers. Immunolocalization studies showed that both diphosphorylated MRLC and Rho-kinase accumulated and colocalized at the contractile ring and the midbody in dividing cells. Taken together, it is suggested that Rho-kinase contributes to MRLC diphosphorylation and reorganization of actin filaments in nonmuscle cells.

L4 ANSWER 18 OF 35 MEDLINE on STN DUPLICATE 9
AN 2002299672 MEDLINE
DN PubMed ID: 11956320
TI Leukotriene D(4) activates MAPK through a Ras-independent but PKCepsilon-dependent pathway in intestinal epithelial cells.
AU Paruchuri Sailaja; Hallberg Bengt; Juhas Maria; Larsson Christer; Sjolander Anita
CS Division of Experimental Pathology, Department of Laboratory Medicine, Lund University, University Hospital Malmo, SE-205 02 Malmo, Sweden.
SO Journal of cell science, (2002 May 1) 115 (Pt 9) 1883-93. Journal code: 0052457. ISSN: 0021-9533.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200212
ED Entered STN: 20020604
Last Updated on STN: 20021217
Entered Medline: 20021211

AB We have recently shown that leukotriene D(4) (LTD(4)) increases cell

survival in intestinal epithelial cells. Here we report and explore the complementary finding that LTD(4) also enhances proliferation in these cells. This proliferative response was approximately half of that induced by epidermal growth factor (EGF) and its required activation of protein kinase C (PKC), Ras and the mitogen-activated protein kinase (MAPK) Erk-1/2. EGF also activated Erk-1/2 in these cells; however the EGF-receptor inhibitor PD153035 did not affect the LTD(4)-induced activation of Erk-1/2. In addition, LTD(4) did not induce **phosphorylation** of the EGF receptor, nor did pertussis toxin (PTX) block EGF-induced activation of Erk-1/2, thus refuting a possible crosstalk between the receptors. Furthermore, LTD(4)-induced, but not EGF-induced, activation of Erk-1/2 was sensitive to PTX, PKC inhibitors and downregulation of PKCepsilon. A definite role for PKCepsilon in LTD(4)-induced stimulation of Erk-1/2 was documented by the inability of LTD(4) to activate Erk-1/2 in cells transfected with either the regulatory domain of PKCepsilon (an isoform specific dominant-negative **inhibitor**) or a **kinase**-dead PKCepsilon. Although Ras and Raf-1 were both transiently activated by LTD(4), only Raf-1 activation was abolished by abrogation of the PKC signal. Furthermore, the LTD(4)-induced activation of Erk-1/2 was unaffected by transfection with dominant-negative N17 Ras but blocked by **transfection** with **kinase**-dead Raf-1. Consequently, LTD(4) regulates the proliferative response by a distinct Ras-independent, PKCepsilon-dependent activation of Erk-1/2 and a parallel Ras-dependent signaling pathway.

L4 ANSWER 19 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:240151 CAPLUS
DN 137:88018
TI Atypical protein kinase C ζ as a target for chemosensitization of tumor cells
AU Filomenko, Rodolphe; Poirson-Bichat, Florence; Billerey, Claire; Belon, Jean-Paul; Garrido, Carmen; Solary, Eric; Bettaieb, Ali
CS INSERM U517, EPHE, Ecole Pratique des Hautes Etudes, IFR, Institut Federatif de Recherche 10, Faculties of Medicine and Pharmacy, Dijon,

21000, Fr.
SO Cancer Research (2002), 62(6), 1815-1821
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Exposure of tumor cells to cytotoxic agents simultaneously activates a variety of intracellular signaling pathways. Some of these pathways involve enzymes from the protein kinase C (PKC) family of serine/threonine kinases. This family includes isoenzymes that neg. influence cell death, whereas other demonstrate an opposite effect. The present study analyzes the role of the ζ atypical PKC isoform in tumor cell response to cytotoxic agents. Using a histone H1 **phosphorylation** assay, we showed that both tumor necrosis factor α and etoposide activate PKCζ in U937 human leukemic cells. Stable **transfection** of a **kinase**-dead, dominant-neg. PKCζ mutant in U937 cells decreases Bcl-2 expression while increasing the expression of Bax and several procaspases. This transfection also prevents etoposide-induced nuclear factor-κB nuclear translocation and accumulation of X-linked inhibitor of apoptosis protein. PKCζ inhibition accelerates the occurrence of apoptosis in leukemic cells exposed to etoposide and tumor necrosis factor α. This sensitization was confirmed in vitro by use of a clonogenic assay. In addition, PKCζ inhibition sensitized tumor cells grown in nude mice to etoposide. These results indicate that PKCζ isoform is a protective signals that is activated in tumor cells exposed to a cytotoxic agent. This inducible resistance factor thus appears an attractive target for chemosensitization of tumor cells.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2002:353785 BIOSIS
DN PREV200200353785
TI Participation of the CaM-kinases in oxidant-induced I-kappaB **phosphorylation** in human T lymphocytes.

AU Howe, Christopher J. [Reprint author]; LaHair, Michelle M. [Reprint
author]; Maxwell, Jill A. [Reprint author]; Lee, John T. [Reprint author];
Robinson, Penni J. [Reprint author]; Rodriguez-Mora, Oswaldo [Reprint
author]; McCubrey, James A. [Reprint author]; Franklin, Richard A.
[Reprint author]
CS Department of Microbiology and Immunology, Brody School of Medicine, East
Carolina University, 600 Moye Blvd., Greenville, NC, 27858, USA
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A316. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on
Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Jun 2002
Last Updated on STN: 26 Jun 2002
AB Cells can be exposed to endogenous oxidants, oxidants produced by nearby
cells, or oxidants induced by certain drugs. Oxidative stress is known to
induce the activation of NF-kappaB, an important transcription factor that
has roles in inflammation, oncogenesis, apoptosis, and viral replication.
We report that the calmodulin antagonist W-7 and the CaM-**kinase**
inhibitors, KN-93 and K252a, block oxidative stress-induced
I-kappaB **phosphorylation** in Jurkat T lymphocytes. In addition,
we report that transient **transfection** of a **kinase**-dead
CaM-KIV construct inhibits I-kappaB **phosphorylation** in response
to oxidative stress. Akt, a reported IkappaK kinase, was phosphorylated
on T308 in response to oxidative stress and this **phosphorylation**
was sensitive to KN-93 inhibition. This result indicates that the
CaM-kinases may be upstream of Akt in this pathway. These findings
demonstrate that the CaM-kinases have a role in oxidative stress-induced
I-kappaB **phosphorylation** and identify the CaM-kinases and
possibly Akt as potential targets that can be used to minimize NF-kappaB
activation in response to oxidative stress.

L4 ANSWER 21 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

STN
AN 2002:313340 BIOSIS
DN PREV200200313340
TI Src kinase mediates phosphoinositide 3-kinase/Akt dependent rapid endothelial nitric oxide synthase activation by estrogen.
AU Haynes, M. Page [Reprint author]; Li, Lei [Reprint author]; Sinha, Diviya [Reprint author]; Russell, Kerry [Reprint author]; Collinge, Mark [Reprint author]; Sessa, William; Bender, Jeffrey [Reprint author]
CS Cardiovascular Medicine, Yale University School of Medicine, 295 Congress Ave, New Haven, CT, 06536, USA
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A206. print. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002. CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting) Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 29 May 2002 Last Updated on STN: 29 May 2002
AB 17beta-estradiol (E2) activates eNOS, enhancing NO release from endothelial cells via the PI3-kinase/Akt pathway. The upstream regulators of this pathway are unknown. We now demonstrate that the Src family **kinase** specific **inhibitor** PP2 abrogates E2- but not ionomycin-stimulated NO release. PP2 blocked E2-induced Akt **phosphorylation**, but did not inhibit NO release from cells transduced with a constitutively active Akt. Additionally, PP2 abrogated E2-induced production of PI3-kinase generated-phosphoinositides indicating that the PP2-inhibitable kinase is upstream of PI3-kinase and Akt. A demonstrated estrogen receptor-c-Src association correlated with rapid E2-induced c-Src **phosphorylation**. Moreover, **transfection** of a **kinase**-dead Src inhibited E2 induced Akt **phosphorylation** whereas constitutively active Src stimulated increased basal Akt **phosphorylation**. Collectively, these data demonstrate that E2 rapidly activates Src kinase resulting in successive activation of PI3-kinase, Akt and eNOS with consequent enhanced NO release. This implicates Src kinase as an important upstream regulator of the E2-stimulated endothelial PI3-kinase/Akt/eNOS pathway.

L4 ANSWER 22 OF 35 MEDLINE on STN DUPLICATE 10
AN 2001696978 MEDLINE
DN PubMed ID: 11746737
TI Antiapoptotic and cytotoxic properties of delta opioid peptide [D-Ala(2),D-Leu(5)]enkephalin in PC12 cells.
AU Hayashi Teruo; Tsao Li-I; Su Tsung-Ping
CS Cellular Pathobiology Unit, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, Maryland 21224, USA.
SO Synapse (New York, N.Y.), (2002 Jan) 43 (1) 86-94. Journal code: 8806914. ISSN: 0887-4476.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20011218
Last Updated on STN: 20020128
Entered Medline: 20020124
AB The delta opioid peptide [D-Ala(2),D-Leu(5)]enkephalin (DADLE) has been shown to promote organ survival and to protect against methamphetamine-induced neurodegeneration. However, the cellular mechanisms of these actions of DADLE are not totally clear. We examined the action of DADLE in serum-deprived pheochromocytoma cells (PC12) and found that DADLE protected against cell death in those cells. However, the dose-response curves of the protective effects of DADLE are U-shaped as judged by three biochemical or morphological assays: the LDH release, the DNA laddering, and the apoptotic nuclei. It was found that femtomolar to picomolar concentrations of DADLE are antiapoptotic, whereas micormolar concentrations of DADLE are cytotoxic in PC12 cells. The protective effect of DADLE could be attenuated by a selective delta2 opioid antagonist and the cytotoxic action of DADLE was reduced by a selective mu opioid receptor antagonist. The treatment of cells with PD98059, a selective **inhibitor** of ERK **kinase** (MEK), or the **transfection** of cells with a dominant interfering form of MEK (MEK-KA97) blocked both the protective effect of DADLE and the ERK **phosphorylation** induced by DADLE. Cytotoxic concentrations of DADLE, on the other hand, caused an increase of Fas-ligand (FasL) in PC12

cells that was attenuated by a selective mu antagonist. Our results suggest, therefore, that endogenous opioid peptides may, at low concentrations, promote cell survival via the MEK-ERK pathway perhaps through delta2 opioid receptors, whereas they may kill cells at high concentrations via the activation of FasL through an as-yet unknown mechanism involving mu opioid receptors.

L4 ANSWER 23 OF 35 MEDLINE on STN DUPLICATE 11
AN 2001512003 MEDLINE
DN PubMed ID: 11445585
TI Atypical lambda/iota PKC conveys 5-lipoxygenase/leukotriene B4-mediated cross-talk between phospholipase A2s regulating NF-kappa B activation in response to tumor necrosis factor-alpha and interleukin-1beta.
AU Anthonsen M W; Andersen S; Solhaug A; Johansen B
CS UNIGEN Center for Molecular Biology, Faculty of Chemistry and Biology, Norwegian University of Science and Technology, N-7491 Trondheim, Norway.
SO Journal of biological chemistry, (2001 Sep 21) 276 (38) 35344-51. Electronic Publication: 2001-07-09. Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010918 Last Updated on STN: 20030105 Entered Medline: 20011025
AB The transcription factor nuclear factor kappaB (NF-kappaB) plays crucial roles in a wide variety of biological functions such as inflammation, stress, and immune responses. We have shown previously that secretory nonpancreatic (snp) and cytosolic (c) phospholipase A(2) (PLA(2)) regulate NF-kappaB activation in response to tumor necrosis factor (TNF)-alpha or interleukin (IL)-1beta activation and that a functional coupling mediated by the 5-lipoxygenase (5-LO) metabolite leukotriene B(4) (LTB(4)) exists between snpPLA(2) and cPLA(2) in human keratinocytes. In this study, we

have further investigated the mechanisms of PLA(2)-modulated NF-kappaB activation with respect to specific kinases involved in TNF-alpha/IL-1beta-stimulated cPLA(2) **phosphorylation** and NF-kappaB activation. The protein **kinase** C (PKC) **inhibitors** RO 31-8220, Go 6976, and a pseudosubstrate peptide inhibitor of atypical PKCs attenuated arachidonic acid release, cPLA(2) **phosphorylation**, and NF-kappaB activation induced by TNF-alpha or IL-1beta, thus indicating atypical PKCs in cPLA(2) regulation and transcription factor activation. **Transfection** of a **kinase**-inactive mutant of lambda/iotaPKC in NIH-3T3 fibroblasts completely abolished TNF-alpha/IL-1beta-stimulated cellular arachidonic acid release and cPLA(2) activation assayed in vitro, confirming the role of lambda/iotaPKC in cPLA(2) regulation. Furthermore, lambda/iotaPKC and cPLA(2) **phosphorylation** was attenuated by phosphatidyinositol 3-**kinase** (PI3-**kinase**) **inhibitors**, which also reduced NF-kappaB activation in response to TNF-alpha and IL-1beta, indicating a role for PI3-kinase in these processes in human keratinocytes. TNF-alpha- and IL-1beta-induced **phosphorylation** of lambda/iotaPKC was attenuated by inhibitors toward snpPLA(2) and 5-LO and by an LTB(4) receptor antagonist, suggesting lambda/iotaPKC as a downstream effector of snpPLA(2) and 5-LO/LTB(4) the LTB(4) receptor. Hence, lambda/iotaPKC regulates snpPLA(2)/LTB(4)-mediated cPLA(2) activation, cellular arachidonic acid release, and NF-kappaB activation induced by TNF-alpha and IL-1beta. In addition, our results demonstrate that PI3-kinase and lambda/iotaPKC are involved in cytokine-induced cPLA(2) and NF-kappaB activation, thus identifying lambda/iotaPKC as a novel regulator of cPLA(2).

L4 ANSWER 24 OF 35 MEDLINE on STN
AN 2001189665 MEDLINE
DN PubMed ID: 11280762
TI Stimulation of beta1 integrin down-regulates ICAM-1 expression and ICAM-1-dependent adhesion of lung cancer cells through focal adhesion kinase.
AU Yasuda M; Tanaka Y; Tamura M; Fujii K; Sugaya M; So T; Takenoyama M; Yasumoto K

CS Second Department of Surgery, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu.
SO Cancer research, (2001 Mar 1) 61 (5) 2022-30.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010425
Last Updated on STN: 20010425
Entered Medline: 20010419
AB Adhesion molecules are involved in intracellular signaling in various physiological and pathological processes including metastasis and growth of tumor cells. Tumor cells interact with various host cells as well as with extracellular matrices through certain adhesion molecules such as integrins. We here propose that stimulation of beta1 integrin reduces intercellular adhesion molecule (ICAM)-1-mediated interaction of lung cancer cells with CTLs. This concept is based on the following findings: (a) engagement of beta1 integrins on certain lung cancer cells by a specific antibody or by ligand matrices such as fibronectin and collagen markedly reduced ICAM-1 expression on the cell surface and induced sICAM-1; (b) down-regulation of ICAM-1 by stimulation of beta1 integrins was abrogated by tyrosine **kinase inhibitors** or by **transfection** of dominant negative truncations of focal adhesion kinase (FAK); (c) engagement of beta1 integrins also reduced ICAM-1-dependent adhesion of lung cancer cells to T cells, a process completely inhibited by tyrosine **kinase inhibitors** and by **transfection** of dominant negative forms of FAK; and (d) stimulation of beta1 integrins prevented killing of lung cancer cells by autologous CTLs. In malignant tumors, cancer cells, including lung cancer cells, are surrounded by extracellular matrix proteins such as fibronectin and collagen. This suggests that the engagement of beta1 integrins by matrix proteins potentially occurs in cancer cells in vivo and that continuous stimulation via beta1 integrins reduces ICAM-1-expression,

ICAM-1-mediated adhesion of cancer cells to CTLs and their killing by CTLs. Our results suggest that such processes can lead to the escape of lung cancer cells in vivo from immunological surveillance.

L4 ANSWER 25 OF 35 MEDLINE on STN DUPLICATE 12
AN 2001514866 MEDLINE
DN PubMed ID: 11562449
TI D(4) dopamine receptor differentially regulates Akt/nuclear factor-kappa b and extracellular signal-regulated kinase pathways in D(4)MN9D cells.
AU Zhen X; Zhang J; Johnson G P; Friedman E
CS Laboratory of Molecular Pharmacology, Department of Pharmacology and Physiology, MCP Hahnemann School of Medicine, Philadelphia, Pennsylvania, USA.
NC DA11029 (NIDA)
NS29514 (NINDS)
SO Molecular pharmacology, (2001 Oct) 60 (4) 857-64.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20010920
Last Updated on STN: 20011008
Entered Medline: 20011004
AB The present study was designed to investigate the role of D(4) dopamine receptors in regulating the Akt/nuclear factor-kappa B (NF-kappa B) and extracellular signal-regulated kinase (ERK) signaling pathways. The D(4) dopamine receptor agonist PD168077 induced time- and dose-dependent activation of Akt and ERK in D(4)MN9D cells that stably express D(4) dopamine receptors. Maximal Akt and ERK stimulation was achieved at 1 microM PD168077. The agonist-mediated stimulations of Akt and ERK were abolished when cells were preincubated with 50 ng/ml PTX or with 1 microM L745,870, a D(4) dopamine receptor antagonist, indicating that activation of the Akt or ERK pathways is mediated by D(4) dopamine receptors and require a pertussis toxin-sensitive G protein. We also detected a time-

and dose-dependent activation of NF-kappa B. Activation of NF-kappa B by 1 microM PD168077 was attenuated in D(4)MN9D cells that were transfected with a kinase-deficient Akt but not in cells transfected with a dominant negative Ras (N17Ras), suggesting that NF-kappa B activation requires Akt but is independent of Ras. In contrast, the transfection of N17Ras into D(4)MN9D cells blunted D(4) dopamine receptor-mediated ERK activation, indicating a Ras-dependent mechanism. Moreover, PP2 (20 nM), an inhibitor of Src, blocked D(4) receptor-mediated SHC **phosphorylation** and ERK activation. In contrast, **transfection** of a **kinase** -dead Akt did not alter D(4) receptor-stimulated ERK. However, PP2 and the mitogen activated protein **kinase kinase inhibitor** PD98059 did not change D(4) receptor-mediated Akt/NF-kappa B activation. All these indicate that distinct mechanisms mediate ERK and Akt/NF-kappa B activation by D(4) dopamine receptor stimulation. We also demonstrated that D(4) receptor-stimulated cell proliferation is mediated by the Src/SHC/Ras/ERK pathway.

L4 ANSWER 26 OF 35 MEDLINE on STN DUPLICATE 13
AN 2001378723 MEDLINE
DN PubMed ID: 11435224
TI Activation of the EGF receptor signaling pathway in airway epithelial cells exposed to Utah Valley PM.
AU Wu W; Samet J M; Ghio A J; Devlin R B
CS Center for Environmental Medicine and Lung Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599, USA.
SO American journal of physiology. Lung cellular and molecular physiology, (2001 Aug) 281 (2) L483-9.
Journal code: 100901229. ISSN: 1040-0605.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB Exposure to ambient particulate matter (PM) in the Utah Valley has

previously been associated with a variety of adverse health effects. To investigate intracellular signaling mechanisms for pulmonary responses to Utah Valley PM inhalation, human primary airway epithelial cells were exposed to aqueous extracts of PM collected from the year before (Y1), during (Y2), and after (Y3) the closure of a local steel mill located in the Utah Valley in this study. **Transfection** with **kinase** -deficient extracellular signal-regulated kinase (ERK) 1 constructs partially blocked Utah Valley PM-induced interleukin (IL)-8 promoter reporter activity. The mitogen-activated protein kinase/ERK **kinase** (MEK) activity **inhibitor** PD-98059 significantly abolished IL-8 released in response to Utah Valley PM, as did the epidermal growth factor (EGF) receptor **kinase inhibitor** AG-1478. Western blotting showed that Utah Valley PM induced **phosphorylation** of EGF receptor tyrosine, MEK1/2, and ERK1/2, which could be ablated with AG-1478 or PD-98059. For all findings, the potency of Utah Valley PM collected during Y2 was found to be lower relative to that of Y1 and Y3. These data demonstrate that Utah Valley PM can induce IL-8 expression partially through the activation of the EGF receptor signaling.

L4 ANSWER 27 OF 35 EMBASE
on STN
AN 2001290758 EMBASE
TI Activation of the EGF receptor signaling pathway in airway epithelial cells exposed to Utah Valley PM.
AU Wu W.; Samet J.M.; Ghio A.J.; Devlin R.B.
CS R.B. Devlin, Human Studies Division, National Health Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC 27711, United States. devlin.robert@epa.gov
SO American Journal of Physiology - Lung Cellular and Molecular Physiology, (2001) Vol. 281, No. 2 25-2, pp. L483-L489.
Refs: 26
ISSN: 1040-0605 CODEN: APLPE7
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy

015 Chest Diseases, Thoracic Surgery and Tuberculosis
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20010906
Last Updated on STN: 20010906
AB Exposure to ambient particulate matter (PM) in the Utah Valley has previously been associated with a variety of adverse health effects. To investigate intracellular signaling mechanisms for pulmonary responses to Utah Valley PM inhalation, human primary airway epithelial cells were exposed to aqueous extracts of PM collected from the year before (Y1), during (Y2), and after (Y3) the closure of a local steel mill located in the Utah Valley in this study. **Transfection** with **kinase** -deficient extracellular signal-regulated kinase (ERK) 1 constructs partially blocked Utah Valley PM-induced interleukin (IL)-8 promoter reporter activity. The mitogen-activated protein kinase/ERK **kinase** (MEK) activity **inhibitor** PD-98059 significantly abolished IL-8 released in response to Utah Valley PM, as did the epidermal growth factor (EGF) receptor **kinase inhibitor** AG-1478. Western blotting showed that Utah Valley PM induced **phosphorylation** of EGF receptor tyrosine, MEK1/2, and ERK1/2, which could be ablated with AG-1478 or PD-98059. For all findings, the potency of Utah Valley PM collected during Y2 was found to be lower relative to that of Y1 and Y3. These data demonstrate that Utah Valley PM can induce IL-8 expression partially through the activation of the EGF receptor signaling.

L4 ANSWER 28 OF 35 EMBASE
on STN
AN 2000157170 EMBASE
TI Serine residues 994 and 1023/25 are important for insulin receptor kinase inhibition by protein kinase C isoforms β2 and θ.
AU Strack V.; Hennige A.M.; Krutzfeldt J.; Bossenmaeir B.; Klein H.-H.; Kellerer M.; Lammers R.; Haring H.-U.
CS Dr. H.-U. Haring, Eberhard-Karls-Universitat, Abt. Innere Medizin IV,

Otfried-Muller-Str. 10, D-72076 Tubingen, Germany
SO Diabetologia, (2000) Vol. 43, No. 4, pp. 443-449.
Refs: 39
ISSN: 0012-186X CODEN: DBTGAJ
CY Germany
DT Journal; Article
FS 003 Endocrinology
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 20000518
Last Updated on STN: 20000518
AB Aims/hypothesis. Inhibition of the signalling function of the human insulin receptor (HIR) is one of the principle mechanisms which induce cellular insulin resistance. It is speculated that serine residues in the insulin receptor β-subunit are involved in receptor inhibition either as inhibitory **phosphorylation** sites or as part of receptor domains which bind inhibitory proteins or tyrosine phosphatases. As reported earlier we prepared 16 serine to alanine point mutations of the HIR and found that serine to alanine mutants HIR-994 and HIR-1023/25 showed increased tyrosine autophosphorylation when expressed in human embryonic kidney (HEK) 293 cells. In this study we examined whether these mutant receptors have a different susceptibility to inhibition by serine kinases or an altered tyrosine kinase activity. Methods. Tyrosine **kinase** assay and **transfection** studies. Results. In an in vitro kinase assay using IRS-1 as a substrate we could detect a higher intrinsic tyrosine kinase activity of both receptor constructs. Additionally, a higher capacity to phosphorylate the adapter protein Shc in intact cells was seen. To test the inhibition by serine kinases, the receptor constructs were expressed in HEK 293 cells together with IRS-1 and protein kinase C isoforms β2 and θ. Phorbol ester stimulation of these cells reduced wild-type receptor autophosphorylation to 58% or 55% of the insulin simulated state, respectively. This inhibitory effect was not observed with HIR-994 and HIR-1023.25, although all other tested HIR mutants showed similar inhibition induced by protein

kinase C. Conclusion/interpretation. The data suggest that the HIR-domain which contains the serine residues 994 and 1023/25 is important for the inhibitory effect of protein kinase C isoforms β2 and θ on insulin receptor autophosphorylation.

L4 ANSWER 29 OF 35 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 1999201897 EMBASE
TI **Phosphorylation** of the transactivation domain of Pax6 by extracellular signal-regulated kinase and p38 mitogen-activated protein kinase.
AU Mikkola I.; Bruun J.-A.; Bjorkoy G.; Holm T.; Johansen T.
CS T. Johansen, Dept. of Biochemistry, Institute of Medical Biology, University of Tromso, 9037 Tromso, Norway. terjej@fagmed.uit.no
SO Journal of Biological Chemistry, (21 May 1999) Vol. 274, No. 21, pp.
15115-15126.
Refs: 76
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 19990701
Last Updated on STN: 19990701
AB The transcription factor Pax6 is required for normal development of the central nervous system, the eyes, nose, and pancreas. Here we show that the transactivation domain (TAD) of zebrafish Pax6 is phosphorylated in vitro by the mitogen-activated protein kinases (MAPKs) extracellular-signal regulated kinase (ERK) and p38 kinase but not by Jun N-terminal kinase (JNK). Three of four putative proline-dependent kinase **phosphorylation** sites are phosphorylated in vitro. Of these sites, the serine 413 (Ser413) is evolutionary conserved from sea urchin to man. Ser413 is also phosphorylated in vivo upon activation of ERK or p38 kinase. Substitution of Ser413 with alanine strongly decreased the transactivation potential of the Pax6 TAD whereas substitution with glutamate increased the transactivation. Reporter gene assays with wild-type and mutant Pax6 revealed that transactivation by the full-length

Pax6 protein from paired domain- binding sites was strongly enhanced (16-fold) following co-**transfection** with activated p38 **kinase**. This enhancement was largely dependent on the Ser413 site. ERK activation, however, produced a 3-fold increase in transactivation which was partly independent of the Ser413 site. These findings provide a starting point for further studies aimed at elucidating a post-translational regulation of Pax6 following activation of MAPK signaling pathways.

L4 ANSWER 30 OF 35 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:725451 CAPLUS
DN 132:30447
TI Transfection of an inducible p16/CDKN2A construct mediates reversible growth inhibition and G1 arrest in the AtT20 pituitary tumor cell line
AU Frost, Simon J.; Simpson, David J.; Clayton, Richard N.; Farrell, William E.
CS Centre for Cell and Molecular Medicine School of Postgraduate Medicine, North Staffordshire Hospital, Keele University, Stoke-on-Trent, ST4 7QB, UK
SO Molecular Endocrinology (1999), 13(11), 1801-1810
CODEN: MOENEN; ISSN: 0888-8809
PB Endocrine Society
DT Journal
LA English
AB Recent studies have shown that methylation of the CpG island within the p16/CDKN2A gene is associated with an absence of p16 protein in human pituitary tumors. However, the effect of restoration of p16 protein expression in this tumor type has not been investigated. In the absence of an available human pituitary cell line we first assessed the suitability of the mouse corticotroph cell line AtT20 as a model system. Initial expts. showed that the p16/CDKN2A gene was not expressed, whereas a transcript for RB1 was detected as assessed by RT-PCR. Further studies showed the p16/CDKN2A gene to be homozygously deleted. The absence of p16/CDKN2A and presence of RB1, the downstream effector of p16-mediated

cell cycle arrest confirmed the suitability of the AtT20 cell line as a model system. Stable transfectants were generated in which p16/CDKN2A is regulated by an inducible promoter. The regulatory effects of p16/CDKN2A expression on cell proliferation were assessed and complemented by fluorescence-activated cell sorting (FACS) anal. of cell cycle profile. Induced expression of p16/CDKN2A resulted in a profound inhibition of cell growth and G1 arrest (80-82%). Western blot anal. showed concomitant expression of p16 protein in arrested cells and a shift in the **phosphorylation** status of pRB toward its hypophosphorylated form. To further confirm that expression of p16/CDKN2A mimicked its in vivo role, reversibility was assessed using alternate cycles in the presence and absence of inducer (isopropyl-1-thio-β-D-galactopyranoside). Over three cycles the absence of induced expression of p16/CDKN2A resulted in release from G1 arrest. These results show that, in a pituitary cell line model, restoration of p16 expression is indeed sufficient to arrest cells in G1 and inhibit cell proliferation and is reversible. Thus restoration of p16 expression through novel strategies, including gene therapy or demethylating agents, may offer successful therapeutic intervention in human forms of this disease.

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 1998:343922 BIOSIS

DN PREV199800343922

TI Applied pressure enhances cell proliferation through mitogen-activated protein kinase activation in mesangial cells.

AU Kawata, Yasunobu; Mizukami, Yoichi [Reprint author]; Fujii, Zenzo; Sakumura, Toshihiro; Yoshida, Ken-Ichi; Matsuzaki, Masunori

CS Dep. Legal Med., Yamaguchi Univ. Sch. Med., 1144 Kogushi, Ube, Yamaguchi 755-8505, Japan

SO Journal of Biological Chemistry, (July 3, 1998) Vol. 273, No. 27, pp.

16905-16912. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 13 Aug 1998
Last Updated on STN: 10 Sep 1998
AB Progressive renal diseases lead to prolonged glomerular hypertension, which induces the proliferation of mesangial cells. This proliferation is thought to be involved in the development of renal injury. Here we investigate mitogen-activated protein kinase (MAPK) activation and cell proliferation in mesangial cells under conditions of high pressure. After pressure-load, the **phosphorylation** level of MAPK (at Tyr-204) increases rapidly with a peak at 1 min, although the amount of MAPK remains almost constant during pressure-load. To confirm the activation of MAPK, we carried out an immunoprecipitation-kinase assay. MAPK activity during pressure-load shows kinetics similar to that of the tyrosine **phosphorylation**. In contrast, c-Jun N-terminal kinase 1 (JNK1) **phosphorylation** falls below basal levels in response to high pressure. Immunocytochemical observations show phosphorylated MAPK in the nucleus at 10 min. The expression of c-Fos, a nuclear transcription factor, is induced by high pressure, and the induction is significantly inhibited by PD98059 (50 muM), an upstream MAPK/extracellular signal-regulated **kinase kinase** (MEK) **inhibitor** of MAPK. The expression of the c-Jun that is induced by JNK1 activation remains unchanged during pressure-load. MAPK **phosphorylation** and cell proliferation by applied pressure are significantly inhibited by genistein, a tyrosine **kinase inhibitor** in a dose-dependent manner, but not by protein **kinase** C **inhibitors**, chelerythrine and GF109203X. Genistein also blocks pressure-induced tyrosine **phosphorylation** of proteins with molecular masses of 35, 53, and 180 kDa. To clarify the physiological role in MAPK activation under high pressure conditions, we transfected antisense MAPK DNA into mesangial cells. The antisense DNA (2 muM) inhibited MAPK expression by 80% compared with expression in the presence of sense or scrambled DNA, and significantly blocked pressure-induced cell proliferation. Treatment of cells with MEK

inhibitor also produced a similar result. MEK inhibitor strongly suppresses DNA synthesis induced by pressure-load. Cyclin D1 expression is significantly increased under high pressure conditions, and the increase is blocked by treatment with MEK inhibitor. These findings show that pressure-load, a novel activator of MAPK, induces the activation of tyrosine kinases, and enhances the proliferation of mesangial cells, probably through cyclin D1 expression.

L4 ANSWER 32 OF 35 MEDLINE on STN DUPLICATE 14
AN 1998417294 MEDLINE
DN PubMed ID: 9746212
TI cAMP-dependent **phosphorylation** and hexamethylene-bis-acetamide induced dephosphorylation of p19 in murine erythroleukemia cells.
AU Scheele J S
CS Department of Chemistry and Biochemistry, University of California San Diego, La Jolla 92093-0612, USA.
SO Molecular and cellular biochemistry, (1998 Aug) 185 (1-2) 55-63.

Journal code: 0364456. ISSN: 0300-8177.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199905
ED Entered STN: 19990607
Last Updated on STN: 19990607
Entered Medline: 19990524
AB The objective of this study was to investigate cyclic-adenosinemonophosphate (cAMP)-dependent **phosphorylation** in murine erythroleukemia (MEL) cells and to identify either direct substrates of cAMP-dependent kinase or downstream effectors of cAMP dependent **phosphorylation** with a potential function in growth and differentiation. MEL-cells rendered deficient in cAMP-dependent protein kinase (A-**kinase**) activity by stable **transfection** with DNA encoding for either a mutant regulatory subunit or a specific peptide **inhibitor** of A-**Kinase** (PKI) are unable to differentiate normally in response to chemical inducers. We have identified by 2-D Western blotting 2 phosphorylated forms of p19, a highly conserved 18-19 kDa cytosolic protein that is frequently upregulated in transformed cells and undergoes

phosphorylation in mammalian cells upon activation of several signal transduction pathways. The **phosphorylation** of the more acidic phosphorylated form is increased in a cAMP-dependent fashion and impaired in cells deficient in cAMP-dependent kinase (A-kinase). Treatment of MEL-cells with the chemical inducer of differentiation hexamethylene-bisacetamide (HMBA) led to dephosphoryation of this phosphoform. Our data are compatible with previous observations which imply that **phosphorylation** of Ser 38 in p19 by p34cdc2-kinase leads to a more basic phosphoform and simultaneous phosphorylation by mitogen-activated kinase of Ser 25 in response to protein kinase C and the cAMP-dependent kinase creates the more acidic species.

L4 ANSWER 33 OF 35 MEDLINE on STN DUPLICATE 15
AN 97042354 MEDLINE
DN PubMed ID: 8887554
TI FGF and stress regulate CREB and ATF-1 via a pathway involving p38 MAP kinase and MAPKAP kinase-2.
AU Tan Y; Rouse J; Zhang A; Cariati S; Cohen P; Comb M J
CS Cell Signaling Laboratory, New England Biolabs, Beverly, MA 01915, USA.
SO EMBO journal, (1996 Sep 2) 15 (17) 4629-42.
Journal code: 8208664. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970128
Last Updated on STN: 20000303
Entered Medline: 19970102
AB Fibroblast growth factor (FGF) activates a protein kinase cascade in SK-N-MC cells that regulates gene expression at a cyclic-AMP response element (CRE) by stimulating the transcriptional activity of CREB. The activation of CREB is prevented by a dominant negative mutant of Ras and triggered via the same site (Ser133) that becomes phosphorylated in response to cyclic AMP and Ca2+. However, the effect of FGF is not mediated by cyclic AMP-dependent protein kinase, TPA-sensitive isoforms of protein kinase-C, p70S6K or p90rsk (all of which phosphorylate CREB at

Ser133 in vitro). Instead, we identify the FGF-stimulated CREB kinase as MAP kinase-activated protein (MAPKAP) kinase-2, an enzyme that lies immediately downstream of p38 MAP kinase, in a pathway that is also stimulated by cellular stresses. We show that MAPKAP kinase-2 phosphorylates CREB at Ser133 in vitro, that the FGF- or stress-induced activation of MAPKAP kinase-2 and **phosphorylation** of CREB and ATF-1 are prevented by similar concentrations of the specific p38 MAP **kinase inhibitor** SB 203580, and that MAPKAP kinase-2 is the only detectable SB 203580-sensitive CREB kinase in SK-N-MC cell extracts. We also show that transfection of RK/p38 MAP kinase in SK-N-MC cells, but not **transfection** of p44 MAP **kinase**, activates Gal4-CREB-dependent transcription via Ser133. These findings identify a new growth factor and stress-activated signaling pathway that regulates gene expression at the CRE.

L4 ANSWER 34 OF 35 MEDLINE on STN DUPLICATE 16
AN 94253131 MEDLINE
DN PubMed ID: 8195196
TI Characterization of Ca2+/calmodulin-dependent protein kinase IV. Role in transcriptional regulation.
AU Enslen H; Sun P; Brickey D; Soderling S H; Klamo E; Soderling T R
CS Vollum Institute, Oregon Health Sciences University, Portland 97201.
NC DK44239 (NIDDK)
GM41292 (NIGMS)
SO Journal of biological chemistry, (1994 Jun 3) 269 (22) 15520-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199406
ED Entered STN: 19940707
Last Updated on STN: 19980206
Entered Medline: 19940630
AB We have characterized Ca2+/calmodulin-dependent protein kinase IV (CaM kinase IV), expressed using the baculovirus/Sf9 cell system, to assess its potential role in Ca2+-dependent transcriptional regulation. CaM kinase IV was strongly inhibited in vitro by KN-62, a specific CaM kinase

inhibitor which suppresses Ca2+-dependent transcription of several genes, so we tested whether CaM kinase IV could stimulate transcription. Co-transfection of COS-1 cells by cDNA for CaM kinase IV gave 3-fold stimulation of a reporter gene expression, whereas co-transfection with CaM **kinase** II gave no transcriptional stimulation. Since this transcriptional response was mediated by **phosphorylation** of cAMP responsive element-binding protein (CREB), we determined the kinetics and site specificities of CaM kinases IV and II for phosphorylating CREB in vitro. CaM kinases IV and II and cAMP kinase (protein kinase A) all had similar Km values for CREB (1-5 microns), but the Vmax of CaM kinase IV was 40-fold lower than those of CaM kinase II and protein kinase A. Although all three kinases phosphorylated Ser133 in CREB, CaM kinase II also gave equal **phosphorylation** of a second site which was not Ser98. The two CREB **phosphorylation** sites were separately 32P-labeled, and the abilities of protein phosphatases 1, 2A, and 2B (calcineurin) to dephosphorylate them were tested. Our results show that all three phosphatases could dephosphorylate both sites, and calcineurin was a stronger catalyst for dephosphorylating site 1 (Ser133) than for site 2. These results indicate that CaM kinase IV may be important in Ca2+-dependent transcriptional regulation through **phosphorylation** of Ser133 in CREB. The fact that CaM kinase II phosphorylates another site in addition to Ser133 in CREB raises the possibility that this second **phosphorylation** site may account for the suppressed **phosphorylation** site may account for the suppressed ability of CaM kinase II to enhance transcription through the CRE/CREB system. In addition multiple protein phosphatases, including calcineurin, may exert a modulatory effect on transcription depending on which site they dephosphorylate.

L4 ANSWER 35 OF 35 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 1992:186312 BIOSIS
DN PREV199293097262; BA93:97262
TI ISOLATION AND CHARACTERIZATION OF RAT 3Y1 FIBROBLAST CLONES OVEREXPRESSING
THE SRC HOMOLOGY REGION OF PHOSPHOLIPASE C-GAMMA-2.
AU HOMMA Y [Reprint author]; EMORI Y; TAKENAWA T
CS DEP BIOL RES, TOKYO METROPOLITAN INST GERONTOL, 35-2 SAKAE, ITABASHI,
TOKYO 173, JPN
SO Journal of Biological Chemistry, (1992) Vol. 267, No. 6, pp. 3778-3782.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
FS BA
LA ENGLISH
ED Entered STN: 13 Apr 1992
Last Updated on STN: 1 Jun 1992
AB To examine the regulatory function of the src-related SH2 and SH3 (SH2/SH3) region of phospholipase C-γ2 (PLC-γ2), we expressed this region of rat PLC-γ2 cDNA in rat 3Y1 fibroblasts and isolated and characterized a number of clones (.apprx. 20 clones). An increase of endogenous tyrosine kinase activity was observed in all cell clones that highly expressed a translational product of the SH2/SH3 domain. Moreover, endogenous phosphatidylinositol 4,5-bisphosphate hydrolyzing activity was also enhanced in these clones, and PLC-γ1 seemed to be preferentially activated among endogenous PLC isozymes. Genistein, an **inhibitor** of tyrosine **kinase**, inhibited this activaiton of PLC-γ1, and tyrosine **phosphorylation** was observed on PLC-γ1 molecules, indicating the involvement of tyrosine kinases in the PLC-γ1 activation. These results suggest that the SH2/SH3 region of PLC-γ would function as a multidirectional regulator which controls at least two major signaling pathways: tyrosine kinase and phosphatidylinositol 4,5-bisphosphate hydrolysis.

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